FORM PTO-1390 (REV 10-95)

U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER: MERCK 2396

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

U S APPLICATION NO (If known, see 37 CFR §1 5): 10/070305

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/08257	24 AUGUST 2000	6 SEPTEMBER 1999

TITLE OF INVENTION

PYRAZOLO [4,3-d] PYRIMIDINES

APPLICANT(S) FOR DO/EO/US

JONAS, Rochus, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ■ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U S C §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ■ A translation of the International Application into English (35 U.S.C. §371(c)(2)).
7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ■ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3))
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C §371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U S.C. §371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R §§3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO (if known, see 37 CFR §1 5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
10/070305	PCT/EP00/08257	MERCK 2396

17. ☒ The following fees are submitted:

	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR §1.492 (a) (1) - (5)):	
Search Report has been prepared by the EPO or JPO..... .... $890.00	
International preliminary examination fee paid to USPTO (37 CFR §1.482).... ... $710 00	
No international preliminary examination fee paid to USPTO (37 CFR §1 482) but international search fee paid to USPTO (37 CFR §1.445(a)(2))..... $740.00	
Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO $1040.00	
International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)..... .... $100.00	

ENTER APPROPRIATE BASIC FEE AMOUNT =					$890.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(e)).					
CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE	
Total claims	9 - 20 =		0	x $ 18.00	$0.00
Independent claims	1 - 3 =		0	x $ 84.00	$0.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ $ 280.00	
TOTAL OF ABOVE CALCULATIONS =					$890.00
Reduction of 1/2 for filing by small entity, if applicable A Verified Small Entity Statement must also be					
SUBTOTAL =					$890.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(f)).					
TOTAL NATIONAL FEE =					$890.00
Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§3.28, 3.31). $40.00 per property.					
TOTAL FEES ENCLOSED =					$890.00
				Amount to be refunded:	
				charged:	

a. ■ A check in the amount of $890.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 13-3402 in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3402. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO: Customer Number 23,599

PATENT TRADEMARK OFFICE

23599

Filed: 5 MARCH 2002

AJZ:kmo

SIGNATURE

Anthony J. Zelano

NAME

27, 969

REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

Jonas et al.

Group Art Unit: TBA

Serial No.: 10/070,305

Examiner: TBA

Filed: March 5, 2002

For: PYRAZOLO [4,3-d] PYRIMIDINES

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

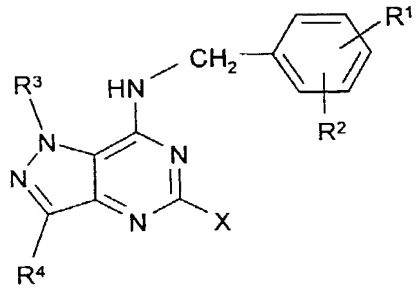
Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE CLAIMS:

Please amend the claims as follows:

1. (Amended) A compound of the formula I



I

in which

R^1 and R^2 are each, independently of one another, H, A, OH, OA or Hal,

R^1 and R^2 together are alternatively alkylene having 3-5 carbon atoms, $-O-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,

R^3 and R^4 are each, independently of one another, H or A,

X is R^5, R^6 or R^7 monosubstituted by R^8,

R^5 is linear or branched alkylene having 1-10 carbon atoms, in which one or two CH_2 groups may be replaced by -CH=CH- groups, O, S or SO,

R^6 is cycloalkyl or cycloalkylalkylene having 5-12 carbon atoms,

R^7 is phenyl or phenylmethyl,

R^8 is COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$ or CN,

A is alkyl having from 1 to 6 carbon atoms, and

Hal is F, Cl, Br or I,

or a physiologically acceptable salt or solvate thereof.

2. (Amended) A compound of the formula I according to Claim 1

(a) 5-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]pentanoic acid;

(b) 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoic acid;

(c) 4-[7-(3,4-methylene[-]dioxy[-]benzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid;

(d) 5-[7-(benzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]pentanoic acid;

(e) [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid;

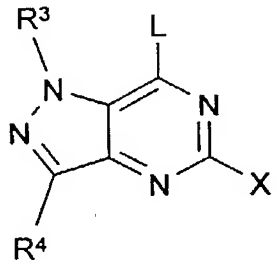
or a physiologically acceptable salt or solvate thereof.

3. (Amended) A process for the preparation

of a compound of the formula I according to Claim 1 and salts thereof,

comprising reacting

a) a compound of the formula II

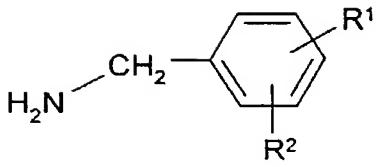


II

in which

R^3, R^4 and X are as defined in Claim 1,
and L is Cl, Br, OH, SCH_3 or a reactive esterified OH group,

with a compound of the formula III



III

in which

R^1 and R^2 are as defined above,

or

b) converting a radical X in a compound of the formula I into another radical X by hydrolysing an ester group to a COOH group or converting a COOH group into an amide or into a cyano group

and/or converting a compound of the formula I into one of its salts.

4. (Amended) A process for the preparation of a pharmaceutical preparation, comprising converting a compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts and solvates into a suitable dosage form together with at least one solid, liquid or semi-liquid excipient or solvent.

5. (Amended) A pharmaceutical preparation, comprising at least one compound of the formula I according to Claim 1 and/or a physiologically acceptable salt or solvate thereof.

6. (Amended) A compound of the formula I according to Claim 1 and physiologically acceptable salt or solvate thereof for combating a disorder of the cardiovascular system and for the treatment and/or therapy of potency disorders.

8. (Amended) Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts and solvates for the preparation of a medicament.

9. (Amended) A method of treating a disease of the cardiovascular system or a potency disorder, comprising administering a compound of claim 1.

REMARKS

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

Anthony J. Zelano Reg. No. 27,969
Attorney for Applicant(s)

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Attorney Docket No.: MERCK-2396

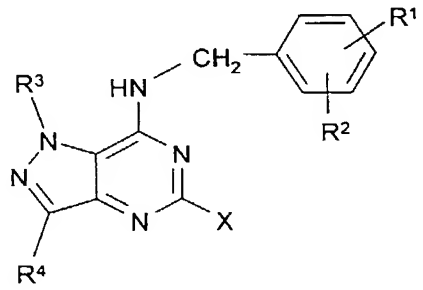
Date: May 31, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend the claims as follows:

1. (Amended) [Compounds] A compound of the formula I



I

in which

R^1[,] and R^2 [in each case] are each, independently of one another, [are] H, A, OH, OA or Hal,

R^1 and R^2 together are alternatively [also] alkylene having 3-5 [C] carbon atoms, -O-CH_2-CH_2-, -CH_2-O-CH_2-, -O-CH_2-O- or -O-CH_2-CH_2-O-,

R^3[,] and R^4 [in each case] are each, independently of one another, [are] H or A,

X is R^5, R^6 or R^7 monosubstituted by R^8,

R^5 is linear or branched alkylene having 1-10 [C] carbon atoms, in which one or two CH_2 groups [can] may be replaced by -CH=CH- groups, O, S or SO,

R^6 is cycloalkyl or cycloalkylalkylene having 5-12 [C] carbon atoms,

R^7 is phenyl or phenylmethyl,

R^8 is COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$ or CN,

A is alkyl having from 1 to 6 [C] carbon atoms, and

Hal is F, Cl, Br or I,

[and their] or a physiologically acceptable [salts and solvates] salt or solvate thereof.

2. (Amended) [Compounds] A compound of the formula I according to Claim 1

(a) 5-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]pentanoic acid;

(b) 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoic acid;

(c) 4-[7-(3,4-methylene[-]dioxy[-]benzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid;

(d) 5-[7-(benzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]pentanoic acid;

(e) [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid;

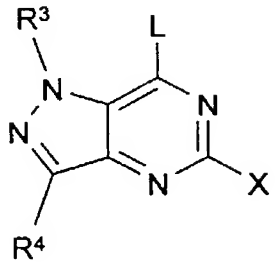
[and their] or a physiologically acceptable [salts and solvates] salt or solvate thereof.

3. (Amended) [Process] A process for the preparation

of [compounds] a compound of the formula I according to Claim 1 and [their] salts thereof,

[characterized in that] comprising reacting

a) a compound of the formula II

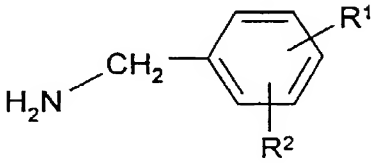


II

in which

R^3, R^4 and X [have the meanings indicated] are as defined in Claim 1,
and L is Cl, Br, OH, SCH_3 or a reactive esterified OH group,

[is reacted] with a compound of the formula III



III

in which

R^1 and R^2 [have the meanings indicated] are as defined above,

or

b) converting a radical X in a compound of the formula I[, a radical X is converted] into another radical X by[, for example,] hydrolysing an ester group to a COOH group or converting a COOH group into an amide or into a cyano group

and/or converting a compound of the formula I [is converted] into one of its salts.

4. (Amended) [Process] A process for the [production] preparation of a pharmaceutical [preparations, characterized in that] preparation, comprising converting a compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts and solvates [is brought] into a suitable [dose] dosage form together with at least one solid, liquid or semi-liquid [vehicle or] excipient or solvent.

5. (Amended) [Pharmaceutical] A pharmaceutical preparation, [characterized in that it contains] comprising at least one compound of the formula I according to Claim 1 and/or [one of its] a physiologically acceptable [salts and solvates] salt or solvate thereof.

6. (Amended) [Compounds] A compound of the formula I according to Claim 1 and [their] physiologically acceptable [salts and solvates] salt or solvate thereof for [the control of diseases] combating a disorder of the cardiovascular system and for the treatment and/or therapy of potency disorders.

8. (Amended) Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts and solvates for the [production] preparation of a medicament.

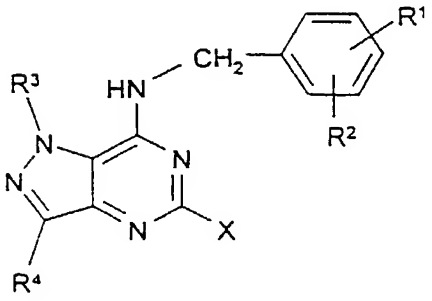
9. (Amended) [Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts and solvates for the production of a medicament for the control of diseases] A method of treating a disease of the cardiovascular system [and for the treatment and/or therapy of] or a potency [disorders] disorder, comprising administering a compound of claim 1.

Merck Patent Gesellschaft
mit beschränkter Haftung
64271 Darmstadt

Pyrazolo[4,3-d]pyrimidines

Pyrazolo[4,3-d]pyrimidines

The invention relates to compounds of the formula I



I

in which

R^1, R^2 in each case independently of one another are H, A, OH, OA or Hal,

R^1 and R^2 together are also alkylene having 3-5 C atoms, $-O-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,

R^3, R^4 in each case independently of one another are H or A,

X is R^5, R^6 or R^7 monosubstituted by R^8,

R^5 is linear or branched alkylene having 1-10 C atoms, in which one or two CH_2 groups can be replaced by -CH=CH- groups, O, S or SO,

R^6 is cycloalkyl or cycloalkylalkylene having 5-12 C atoms,

R^7 is phenyl or phenylmethyl,

R^8 is COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$ or CN,

A is alkyl having 1 to 6 C atoms and

Hal is F, Cl, Br or I,

and their physiologically acceptable salts and solvates.

Pyrimidine derivatives are disclosed, for example, in EP 201 188 and WO 93/06104.

The invention was based on the object of finding novel compounds having valuable properties, in particular those which can be used for the production of medicaments.

It has been found that the compounds of the formula I and their salts have very valuable pharmacological properties together with good tolerability.
In particular, they exhibit specific inhibition of cGMP phosphodiesterase (PDE V).

Quinazolines having cGMP phosphodiesterase-inhibiting activity are described, for example, in J. Med. Chem. 36, 3765 (1993) and ibid. 37, 2106 (1994).

The biological activity of the compounds of the formula I can be determined by methods such as are described, for example, in WO 93/06104. The affinity of the compounds according to the invention for cGMP and cAMP phosphodiesterase is determined by the determination of their IC_{50} values (concentration of the inhibitor which is needed in order to achieve a 50% inhibition of the enzyme activity).
For carrying out the determinations, enzymes isolated according to known methods can be used (e.g. W.J. Thompson et al., Biochem. 1971, 10, 311). For carrying out the experiments, a modified batch method of W.J. Thompson and M.M. Appleman (Biochem. 1979, 18, 5228) can be used.

The compounds are therefore suitable for the treatment

of disorders of the cardiovascular system, in particular of cardiac insufficiency, and for the treatment and/or therapy of potency disorders (erectile dysfunction).

The use of substituted pyrazolopyrimidinones for the treatment of impotence is described, for example, in WO 94/28902.

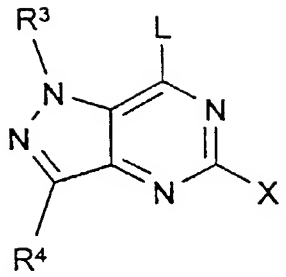
The compounds are efficacious as inhibitors of the phenylephrine-induced contractions in corpus cavernosum preparations from hares.
This biological action can be demonstrated, for example, according to the method which is described by F. Holmquist et al. in J. Urol., 150, 1310-1315 (1993).
The inhibition of the contraction shows the efficacy of the compounds according to the invention for the therapy and/or treatment of potency disorders.

The compounds of the formula I can be employed as pharmaceutical active compounds in human and veterinary medicine. They can furthermore be employed as intermediates for the preparation of further pharmaceutical active compounds.

The invention accordingly relates to the compounds of the formula I and to a process for the preparation of compounds of the formula I according to Claim 1 and their salts,

which is characterized in that

a) a compound of the formula II



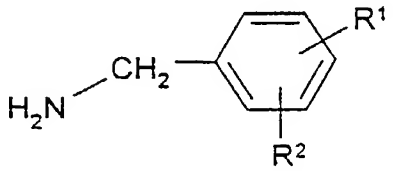
II

in which

R^3, R^4 and X have the meanings indicated,

and L is Cl, Br, OH, SCH_3 or a reactive esterified OH group,

is reacted with a compound of the formula III



III

in which

R^1 and R^2 have the meanings indicated,

or

b) in a compound of the formula I, a radical X is converted into another radical X by, for example, hydrolysing an ester group to a COOH group or converting a COOH group into an amide or into a cyano group

and/or a compound of the formula I is converted into one of its salts.

Solvates of the compounds of the formula I are understood as meaning adducts of inert solvent molecules to

the compounds of the formula I which are formed on account of their mutual attractive force. Solvates are, for example, mono- or dihydrates or alcoholates.

Above and below, the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and L have the meanings indicated in the formulae I, II and III, if not expressly stated otherwise.

A is alkyl having 1-6 C atoms.

In the above formulae, alkyl is preferably unbranched and has 1, 2, 3, 4, 5 or 6 C atoms and is preferably methyl, ethyl or propyl, furthermore preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also n-pentyl, neopentyl, isopentyl or hexyl.

X is an R^5, R^6 or R^7 radical monosubstituted by R^7.

R^5 is a linear or branched alkylene radical having 1-10 C atoms, where the alkylene radical is preferably, for example, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, sec-butylene, pentylene, 1-, 2- or 3-methylbutylene, 1,1-, 1,2- or 2,2-dimethylpropylene, 1-ethylpropylene, hexylene, 1-, 2-, 3- or 4-methylpentylene, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutylene, 1- or 2-ethylbutylene, 1-ethyl-1-methylpropylene, 1-ethyl-2-methylpropylene, 1,1,2- or 1,2,2-trimethylpropylene, linear or branched heptylene, octylene, nonylene or decylene. R^5 is furthermore, for example, but-2-enylene or hex-3-enylene.

A CH_2 group in R^5 can preferably be replaced by oxygen. Ethylene, propylene, butylene or CH_2-O-CH_2 is very particularly preferred.

R^6 is cycloalkylalkylene having 5-12 C atoms, preferably, for example, cyclopentylmethylene, cyclohexylmethylene, cyclohexylethylene, cyclohexylpropylene or cyclohexylbutylene.

R^6 is also cycloalkyl preferably having 5-7 C atoms. Cycloalkyl is, for example, cyclopentyl, cyclohexyl or

cycloheptyl.

Hal is preferably F, Cl or Br, but also I.

The radicals R^1 and R^2 can be identical or different and are preferably in the 3 or 4 position of the phenyl ring. They are, for example, in each case independently of one another, H, alkyl, OH, F, Cl, Br or I or together alkylene, such as, for example, propylene, butylene or pentylene, furthermore ethylenoxy, methylenedioxy or ethylenedioxy. Preferably, they are also in each case alkoxy, such as, for example, methoxy, ethoxy or propoxy.

The radical R^8 is preferably, for example, COOH, COOA such as, for example, $COOCH_3$ or $COOC_2H_5$, $CONH_2$, $CON(CH_3)_2$, $CONHCH_3$ or CN, but in particular COOH or COOA.

It applies to the entire invention that all radicals which occur a number of times can be identical or different, i.e. are independent of one another.

Accordingly, the invention in particular relates to those compounds of the formula I in which at least one of the radicals mentioned has one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following subformulae Ia to If, which correspond to the formula I and in which the radicals not designated in greater detail have the meanings indicated in the formula I, but in which

in Ia X is R^5 substituted by COOH, COOA, $CONH_2$, $CONA_2$, CONHA or CN, or is phenyl or phenylmethyl;

in Ib R^1 and R^2 together are alkylene having 3-5 C atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or

			$-O-CH_2-CH_2-O-$,
		X	is R^5 substituted by COOH, COOA, $CONH_2$, $CONA_2$, CONHA or CN, or is phenyl or phenylmethyl;
	in Ic	R^1, R^2	in each case independently of one another are H, A, OH, OA or Hal,
		R^1 and R^2	together are also alkylene having 3-5 C atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,
		X	is R^5 substituted by COOH, COOA, $CONH_2$, $CONA_2$, CONHA or CN, or is phenyl or phenylmethyl;
	in Id	R^1, R^2	in each case independently of one another are H, A, OH, OA or Hal,
		R^1 and R^2	together are also alkylene having 3-5 C atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,
		X	is alkylene having 2-5 C atoms, which is monosubstituted by R^8, or cyclohexyl, phenyl or phenylmethyl,
		R^3	is alkyl having 1-6 C atoms,
		R^4	is alkyl having 1-6 C atoms,
		R^8	is COOH or COOA,
		A	is alkyl having 1 to 6 C atoms,
		Hal	is F, Cl, Br or I;
	in Ie	R^1, R^2	in each case independently of one another are H, A, OH, OA or Hal,
		R^1 and R^2	together are also alkylene having 3-5 C atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,
		R^3	is alkyl having 1-6 C atoms,
		R^4	is alkyl having 1-6 C atoms,
		X	is $-(CH_2)_{2-5}-R^8$, 4-R^8-cyclohexyl, 4-R^8-phenyl or 4-(R^8-methyl)phenyl;
	in If	R^1, R^2	in each case independently of one

another are H, A, OH, OA or Hal,

R^1 and R^2 together are also alkylene having 3-5 C atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,

R^3 is alkyl having 1-6 C atoms,

R^4 is alkyl having 1-6 C atoms,

X is $-(CH_2)_{2-5}-R^8$, in which one CH_2 group can be replaced by O, or is 4-R^8-cyclohexyl, 4-R^8-phenyl or 4-(R^8-methyl)phenyl,

R^8 is COOH or COOA.

The compounds of the formula I and also the starting substances for their preparation are otherwise prepared by methods known per se, such as are described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der organischen Chemie [Methods of organic chemistry], Georg-Thieme-Verlag, Stuttgart), namely under reaction conditions which are known and suitable for the reactions mentioned. In this case, use can also be made of variants which are known per se, but not mentioned here in greater detail.

In the compounds of the formula II or III, R^1, R^2, R^3, R^4 and X have the meanings indicated, in particular the preferred meanings indicated.

If L is a reactive esterified OH group, this is preferably alkylsulfonyloxy having 1-6 C atoms (preferably methylsulfonyloxy) or arylsulfonyloxy having 6-10 C atoms (preferably phenyl- or p-tolyl-sulfonyloxy, furthermore also 2-naphthalene-sulfonyloxy).

The compounds of the formula I can preferably be obtained by reacting compounds of the formula II with compounds of the formula III.

If desired, the starting substances can also be formed

in situ, such that they are not isolated from the reaction mixture but immediately reacted further to give the compounds of the formula I.
On the other hand, it is possible to carry out the reaction stepwise.

As a rule, the starting compounds of the formulae II and III are known. If they are not known, they can be prepared by methods known per se.
Compounds of the formula II can be prepared according to methods known from the literature, e.g. from 4-amino-3-alkoxycarbonylpyrazoles by cyclization with nitriles and subsequent reaction of the cyclization products with phosphorus oxychloride (analogous to Houben Weyl E9b/2).

In detail, the reaction of the compounds of the formula II with the compounds of the formula III is carried out in the presence or absence of an inert solvent at temperatures between approximately -20 and approximately 150°, preferably between 20 and 100°.

The addition of an acid-binding agent, for example of an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or of another salt of a weak acid of the alkali metals or alkaline earth metals, preferably of potassium, sodium or calcium, or the addition of an organic base such as triethylamine, dimethylamine, pyridine or quinoline or of an excess of the amine component can be favourable.

Suitable inert solvents are, for example, hydrocarbons such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol

ethers such as ethylene glycol monomethyl or monoethyl ether (methyl glycol or ethyl glycol), ethylene glycol dimethyl ether (diglyme); ketones such as acetone or butanone; amides such as acetamide, dimethylacetamide, N-methylpyrrolidone or dimethylformamide (DMF); nitriles such as acetonitrile; sulfoxides such as dimethyl sulfoxide (DMSO); nitro compounds such as nitromethane or nitrobenzene; esters such as ethyl acetate or mixtures of the solvents mentioned.

It is furthermore possible to convert a radical X into another radical X in a compound of the formula I, e.g, by hydrolysing an ester or a cyano group to a COOH group.

Ester groups can be hydrolysed, for example, using NaOH or KOH in water, water/THF or water/dioxane at temperatures between 0 and 100°.

Carboxylic acids can be converted, for example, using thionyl chloride into the corresponding carbonyl chlorides and these can be converted into carboxamides. Carbonitriles are obtained from these in a known manner by dehydration.

An acid of the formula I can be converted into the associated acid addition salt using a base, for example by reaction of equivalent amounts of the acid and the base in an inert solvent such as ethanol and subsequent evaporation. Suitable bases for this reaction are those which yield physiologically acceptable salts.

Thus the acid of the formula I can be converted into the corresponding metal salts, in particular alkali metal or alkaline earth metal salts, or into the corresponding ammonium salt, using a base (e.g. sodium or potassium hydroxide or carbonate).

For this reaction, suitable organic bases are in particular also those which yield physiologically acceptable salts, such as, for example, ethanolamine.

On the other hand, a base of the formula I can be con-

verted into the associated acid addition salt using an acid, for example by reaction of equivalent amounts of the base and of the acid in an inert solvent such as ethanol and subsequent evaporation. For this reaction, suitable acids are in particular those which yield physiologically acceptable salts. Thus inorganic acids can be used, e.g. sulfuric acid, nitric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, e.g. formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemono- and -disulfonic acids and laurylsulfuric acid. Salts with physiologically unacceptable acids, e.g. picrates, can be used for the isolation and/or purification of the compounds of the formula I.

The invention furthermore relates to the use of the compounds of the formula I and/or their physiologically acceptable salts for the production of pharmaceutical preparations, in particular by a non-chemical route. In this case, they can be brought into a suitable dose form together with at least one solid, liquid and/or semi-liquid vehicle or excipient and, if appropriate, in combination with one or more further active compounds.

The invention also relates to medicaments of the formula I and their physiologically acceptable salts as phosphodiesterase V inhibitors.

The invention furthermore relates to pharmaceutical preparations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts.

These preparations can be used as medicaments in human or veterinary medicine. Possible vehicles are organic or inorganic substances which are suitable for enteral (e.g. oral) or parenteral administration or topical application and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. In particular, tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops are used for oral administration, suppositories are used for rectal administration, solutions, preferably oily or aqueous solutions, furthermore suspensions, emulsions or implants, are used for parenteral administration and ointments, creams or powders are used for topical application. The novel compounds can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection preparations. The preparations indicated can be sterilized and/or can contain excipients such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colourants, flavourings and/or one or more further active compounds, e.g. one or more vitamins.

The compounds of the formula I and their physiologically acceptable salts can be used in the control of diseases in which an increase in the cGMP (cyclic guanosine monophosphate) level leads to inhibition or prevention of inflammation and muscle relaxation. The compounds according to the invention can particularly be used in the treatment of diseases of the cardio-

vascular system and for the treatment and/or therapy of potency disorders.

In this case, as a rule the substances are preferably administered in doses of between approximately 1 and 500 mg, in particular between 5 and 100 mg, per dose unit. The daily dose is preferably between approximately 0.02 and 10 mg/kg of body weight. The specific dose for each patient depends, however, on all sorts of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and route of administration, on the excretion rate, pharmaceutical combination and severity of the particular disorder to which the therapy applies. Oral administration is preferred.

Above and below, all temperatures are indicated in °C. In the following examples, "customary working up" means: if necessary, water is added, the mixture is adjusted, if necessary, depending on the constitution of the final product, to a pH of between 2 and 10 and extracted with ethyl acetate or dichloromethane, the organic phase is separated off, dried over sodium sulfate and evaporated, and the residue is purified by chromatography on silica gel and/or by crystallization.

Mass spectrometry (MS): EI (electron impact ionization) M^+
FAB (fast atom bombardment) $(M+H)^+$

Example 1

3 g of methyl 3-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionate and 1.9 g of 3-chloro-4-methoxybenzylamine ("A") in 50 ml of dimethylformamide (DMF) are stirred at 60° for 12 hours in the presence of potassium carbonate. After filtration, the solvent is removed and the mixture is worked up in the customary manner. 4.6 g of methyl

3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionate are obtained as a colourless oil.

The following is obtained analogously by reaction of "A"

with methyl 2-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]acetate

methyl 2-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]acetate.

The following is analogously obtained by reaction of 3,4-methylenedioxybenzylamine

with methyl 3-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]propionate

methyl 3-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionate.

The following is analogously obtained by reaction of "A"

with methyl 4-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]butyrate

methyl 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyrate.

The following is analogously obtained by reaction of 3,4-methylenedioxybenzylamine

with methyl 4-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]butyrate

methyl 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyrate.

The following is analogously obtained by reaction of "A"

with methyl 5-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]valerate
methyl 5-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valerate.

The following is analogously obtained by reaction of 3,4-methylenedioxybenzylamine

with methyl 5-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]valerate
methyl 5-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valerate.

The following is analogously obtained by reaction of "A"

with methyl 7-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]heptanoate
methyl 7-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]heptanoate.

The following is analogously obtained by reaction of 3,4-methylenedioxybenzylamine

with methyl 7-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]heptanoate
methyl 7-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]heptanoate.

The following is analogously obtained by reaction of "A"

with methyl 2-[4-(7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl-)cyclohex-1-yl]acetate
methyl 2-{4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetate.

The following is analogously obtained by reaction of 3,4-methylenedioxybenzylamine

with methyl 2-[4-(7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohex-1-yl]acetate
methyl 2-{4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetate.

The following are analogously obtained by reaction of benzylamine

with methyl 3-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]propionate
methyl 3-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionate;

with methyl 4-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]butyrate
methyl 4-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyrate;

with methyl 5-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]valerate
methyl 5-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valerate.

The following is analogously obtained by reaction of "A"

with methyl 4-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]-cyclohexanecarboxylate

methyl 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexanecarboxylate

and the following is analogously obtained by reaction of 3,4-methylenedioxybenzylamine

methyl 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexanecarboxylate.

Example 2

4.3 g of methyl 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]-propionate are dissolved in 30 ml of tetrahydrofuran (THF) and, after addition of 10 ml of 10% NaOH, stirred at 60° for 8 hours. After addition of 10% HCl, the deposited crystals are separated off and recrystallized from methanol. 3.7 g of 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionic acid, m.p. 178°, are obtained.

By evaporation with the equivalent amount of methanolic potassium hydroxide solution, the potassium salt of the acid is obtained as an amorphous powder.

Analogously, from the esters mentioned in Example 1, the compounds

2-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]acetic acid,

3-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionic acid,

4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 152°;

4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 172°;

5-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valeric acid, m.p. 159°;

5-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valeric acid, ethanolamine salt, m.p. 160°;

7-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]heptanoic acid,

7-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]heptanoic acid,

2-{4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

2-{4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

3-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]propionic acid,

4-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]butyric acid,

5-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]valeric acid, m.p. 185°;

4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-

3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexane-carboxylic acid,

4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexane-carboxylic acid,

are obtained.

Analogously, the compounds

5-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-isopropyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valeric acid, cyclohexylamine salt, m.p. 148°;

4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-ethyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 176°;

4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-ethyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 187°;

4-[7-(3-chloro-4-methoxybenzylamino)-1-ethyl-3-methyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 206°;

4-[7-(3,4-methylenedioxybenzylamino)-1-ethyl-3-methyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 177°;

4-[7-benzylamino-1-methyl-3-ethyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 208°;

4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-methyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 250°;

4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-

3-methyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 225°;

4-[7-benzylamino-1-methyl-3-methyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 201°;

5-[7-(4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valeric acid, m.p. 160°;

5-[7-(3-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valeric acid, m.p. 141°;

5-[7-(4-chlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valeric acid, m.p. 148°;

5-[7-(3-chlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valeric acid, m.p. 151°;

are obtained.

Example 3

A mixture of 1.8 g of methyl 4-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]phenylcarboxylate ("B") and 1.5 g of 3-chloro-4-methoxybenzylamine in 20 ml of N-methylpyrrolidone is heated at 110° for 4 hours. After cooling, it is worked up in the customary manner. 2.2 g of methyl 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]benzoate are obtained.

Analogously to Example 2, from 1.2 g of the ester, 1.0 g of

4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoic acid,

ethanolamine salt, m.p. 139°
is obtained.

Analogously to Example 1, from "B" and 3,4-methylenedioxybenzylamine
methyl 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoate and, therefrom, by ester hydrolysis
4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoic acid
are obtained.

Analogously, the compounds
4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]phenylacetic acid, glucamine salt, m.p. 114°
and
4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]phenylacetic acid
are obtained.

Example 4

1 equivalent of 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]-propionic acid and 1.2 equivalents of thionyl chloride are stirred in dichloromethane for 2 hours. The solvent is removed and 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]-propionyl chloride is obtained. The product is transferred to aqueous ammonia, stirred for one hour and, after customary working up, 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-yl]propionamide is obtained.

Example 5

1 equivalent of DMF and 1 equivalent of oxalyl chloride

are dissolved in acetonitrile at 0°. 1 equivalent of 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionamide is then added. The mixture is stirred for one hour. After customary working up, 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-yl]propionitrile is obtained.

Example 6

Analogously to Examples 1, 2 and 3, by reaction of the corresponding chloropyrimidine derivatives with 3,4-ethylenedioxybenzylamine, the carboxylic acids below are obtained

4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid,

3-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionic acid,

5-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valeric acid,

7-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]heptanoic acid,

2-{4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexanecarboxylic acid,

4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoic acid,

4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoic acid,

4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]phenylacetic acid.

Analogously, by reaction with 3,4-dichlorobenzylamine the compounds below

4-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 209°,

3-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionic acid,

5-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valeric acid,

7-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]heptanoic acid,

2-{4-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

4-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexanecarboxylic acid,

4-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoic acid,

4-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]phenylacetic acid,

are obtained.

Analogously, by reaction with 3-chloro-4-ethoxybenzylamine the compounds below

4-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid,

3-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionic acid,

5-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valeric acid,

7-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]heptanoic acid,

2-{4-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

4-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexane-carboxylic acid,

4-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoic acid,

4-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]phenylacetic acid,

are obtained.

Analogously, by reaction with 3-chloro-4-isopropoxybenzylamine the compounds below

4-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-

3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid,

3-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionic acid,

5-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valeric acid,

7-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]heptanoic acid,

2-{4-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

4-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexane-carboxylic acid,

4-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoic acid,

4-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]phenylacetic acid,

are obtained.

Example 7

Analogously to Examples 1 and 2, the compound

[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid, ethanolamine salt, m.p. 138°,

is obtained.

The following examples relate to pharmaceutical preparations:

Example A: Injection vials

A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogenphosphate is adjusted to pH 6.5 in 3 l of double-distilled water using 2 N hydrochloric acid, sterile filtered, dispensed into injection vials, lyophilized under sterile conditions and aseptically sealed. Each injection vial contains 5 mg of active compound.

Example B: Suppositories

A mixture of 20 g of active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

Example C: Solution

A solution is prepared from 1 g of an active compound of the formula I, 9.38 g of $NaH_2PO_4 \cdot 2\ H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12\ H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water. It is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of an active compound of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of active compound of the formula I,

4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed in a customary manner to give tablets such that each tablet contains 10 mg of active compound.

Example F: Coated tablets

Analogously to Example E, tablets are pressed and are then coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth and colourant.

Example G: Capsules

2 kg of active compound of the formula I are dispensed in a customary manner into hard gelatin capsules such that each capsule contains 20 mg of the active compound.

Example H: Ampoules

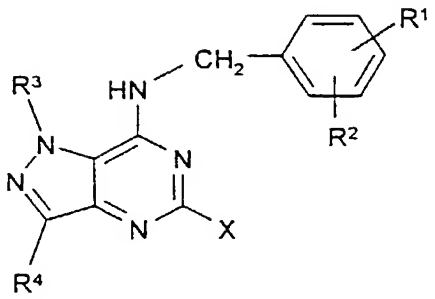
A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is sterile filtered, dispensed in ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.

Example I: Inhalation spray

14 g of active compound of the formula I are dissolved in 10 l of isotonic NaCl solution and the solution is filled into commercially available spray containers having a pump mechanism. The solution can be sprayed into the mouth or nose. One puff of spray (approximately 0.1 ml) corresponds to a dose of approximately 0.14 mg.

Patent Claims

1. Compounds of the formula I



I

in which

R^1, R^2 in each case independently of one another are H, A, OH, OA or Hal,

R^1 and R^2 together are also alkylene having 3-5 C atoms, $-O-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,

R^3, R^4 in each case independently of one another are H or A,

X is R^5, R^6 or R^7 monosubstituted by R^8,

R^5 is linear or branched alkylene having 1-10 C atoms, in which one or two CH_2 groups can be replaced by -CH=CH- groups, O, S or SO,

R^6 is cycloalkyl or cycloalkylalkylene having 5-12 C atoms,

R^7 is phenyl or phenylmethyl,

R^8 is COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$ or CN,

A is alkyl having 1 to 6 C atoms and

Hal is F, Cl, Br or I,

and their physiologically acceptable salts and solvates.

2. Compounds of the formula I according to Claim 1

(a) 5-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]pentanoic acid;
(b) 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoic acid;
(c) 4-[7-(3,4-methylene-dioxy-benzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid;
(d) 5-[7-(benzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]pentanoic acid

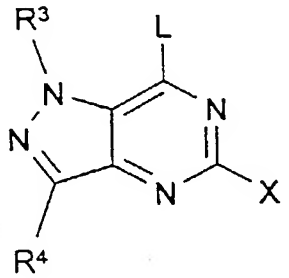
and their physiologically acceptable salts and solvates.

3. Process for the preparation

of compounds of the formula I according to Claim 1 and their salts,

characterized in that

a) a compound of the formula II



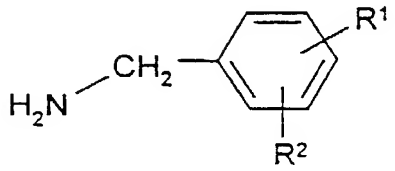
II

in which

R^3, R^4 and X have the meanings indicated in Claim 1,

and L is Cl, Br, OH, SCH_3 or a reactive esterified OH group,

is reacted with a compound of the formula III



III

in which

R^1 and R^2 have the meanings indicated,

or

b) in a compound of the formula I, a radical X is converted into another radical X by, for example, hydrolysing an ester group to a COOH group or converting a COOH group into an amide or into a cyano group

and/or a compound of the formula I is converted into one of its salts.

4. Process for the production of pharmaceutical preparations, characterized in that a compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts and solvates is brought into a suitable dose form together with at least one solid, liquid or semi-liquid vehicle or excipient.

5. Pharmaceutical preparation characterized in that it contains at least one compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts and solvates.

6. Compounds of the formula I according to Claim 1 and their physiologically acceptable salts and solvates for the control of diseases of the cardiovascular system and for the treatment and/or therapy of potency disorders.

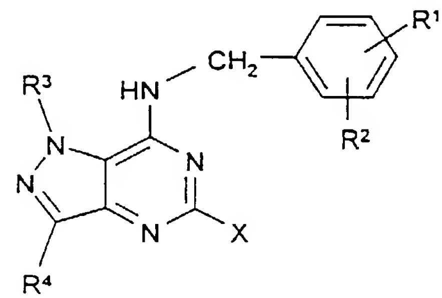
7. Medicaments of the formula I according to Claim 1 and their physiologically acceptable salts and solvates as phosphodiesterase V inhibitors.

8. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts and solvates for the production of a medicament.

9. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts and solvates for the production of a medicament for the control of diseases of the cardiovascular system and for the treatment and/or therapy of potency disorders.

Abstract

Pyrazolo[4,3-d]pyrimidines of the formula I



I

and their physiologically acceptable salts,

in which

R^1, R^2, R^3, R^4 and X have the meanings indicated in Claim 1, exhibit phosphodiesterase V inhibition and can be employed for the treatment of disorders of the cardiovascular system and for the treatment and/or therapy of potency disorders.

Attorney Docket Number: MERCK 2396

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PYRAZOLO[4,3-d]PYRIMIDINES

the specification of which

- ☐ is attached hereto
- ☐ was filed on 24 August 2000 as United States Application Number or PCT International Application Number PCT/EP00/08257 and (if applicable) was amended on _____

I hereby authorize our attorneys to insert the serial number assigned to this application.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 USC §119			
APPLICATION NO.	COUNTRY	DAY/MONTH/YEAR FILED	PRIORITY CLAIMED
19942474.8	GERMANY	6 SEPTEMBER 1999	YES

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)	
APPLICATION NUMBER	FILING DATE

I hereby claim the benefit under 35 U.S.C. §120 of any United States application, or §365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

PRIOR U.S./PCT INTERNATIONAL APPLICATION(S) DESIGNATED FOR BENEFIT UNDER 37 U.S.C. §120		
APPLICATION NO.	FILING DATE	STATUS — PATENTED, PENDING, ABANDONED

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith: I. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Alan E.J. Branigan (20,565); John R. Moses (24,983); Harry B. Shubin (32,004); Brion P. Heaney (32,542); Richard J. Traverso (30,595); John A. Sopp (33,103); Richard M. Lebovitz (37,067); John H. Thomas (33,460); Catherine M. Joyce (40,668); Nancy J. Axelrod (44,014); James T. Moore (35,619); James E. Ruland (37,432); Jennifer J. Branigan (40,921) and Robert E. McCarthy (46,044)

Send Correspondence to Customer Number 23599

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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☐ Additional joint inventors are named on separately numbered sheets attached hereto.